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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,318	10/03/2001	Dominic E. Cosgrove	249.0002 0101	1885

26813 7590 01/21/2004

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EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 01/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,318	COSGROVE, DOMINIC E.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *8-14 and 24-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/30/2003* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7 and 15-23, drawn to a method of determining whether an individual has or is at risk for developing Usher syndrome Type IIa, classified in class 435, subclass 7.94.

II. Claims 8-14, drawn to a method for detecting the presence or absence of an usherin protein, classified in class 435, subclass 7.8.

III. Claim 24-29, 38-41, drawn to a test kit for detecting the presence or absence of Usher syndrome Type IIa in an individual comprising an antibody and a detectably labeled usherin protein, classified in class 436, subclass 545.

IV. Claims 30-41, drawn to a test kit for detecting the presence or absence of Usher syndrome Type IIa in an individual comprising a first antibody that immunoreacts with usherin protein and a second antibody that ummunoreacts with a portion of a human usherin protein, classified in class 436, subclass 548.

2. The inventions are distinct, each from the other because of the following reasons:

3. Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In

the instant case the different inventions I and II have different functions and modes of operation. In particular, invention I is drawn to a method of determining if an individual has or is at risk for developing Usher syndrome Type IIa, while invention II is drawn to determining if the presence of a usherin protein. Furthermore, while both methods require an antibody immunoreactive to at least a portion of a human usherin protein, invention I is directed more toward correlating the presence of polypeptides immunoreactive with the antibody with the absence of Usher syndrome Type IIa and the absence of protein or proteins immunoreactive with the antibody with the presence of Usher syndrome Type IIa, while invention II is directed more toward correlating the presence of the immunoconjugate with the presence of all polypeptides immunoreactive with the antibody, defined by applicant as usherin proteins.

4. Inventions III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions have different modes of operation. The invention of group III has comprised of a single antibody that reacts with a human usherin protein and a detectably labeled usherin protein, while the invention of group IV is comprised of a first and second antibody that immunoreacts with a portion of human usherin protein.

5. Inventions I, II and III, IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the methods of

inventions I and II can be performed by a variety of assays, such as flow cytometry, ELISA, etc, while inventions III and IV can be used as surface specific adhesives or filters.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and the search required for one group is not required for others, restriction for examination purposes as indicated is proper.

7. During a telephone conversation with Ann Mueting on December 17, 2003 a provisional election was made with traverse to prosecute the invention of group I, claims 1-7 and 15-23. Affirmation of this election must be made by applicant in replying to this Office action. Claims 8-14 and 24-41 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

8. Claim 2 is objected to because of the following informalities: a space is missing between the words group and consisting. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-7, 15-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. In claims 1 and 15, applicant recites the limitation of a complement of a polynucleotide encoding the usherin protein is capable of hybridizing to the polynucleotide represented by SEQ ID NO: 3, rendering the claims indefinite. It is unclear whether the purpose of this limitation is to define an usherin protein as anything with a complementary polynucleotide sequence that would hybridize SEQ ID NO: 3. Furthermore, it is unclear whether the "complement of any of the polynucleotide encoding the usherin protein" itself would include only full-length complements or would include any complement which would vary in length and chemical structure. Currently, this limitation can be interpreted as usherin protein represented by SEQ ID NO: 3, or as anything with a complementary polynucleotide sequence that would hybridize SEQ ID NO: 3, where the complement would include any complement.

12. In claim 2, applicant recites the limitation where the biological sample is selected from a group including a portion of testis, ovary, placenta, and combinations thereof. It is unclear how an individual would have both testis and ovaries and a placenta. Although applicant has defined the term "an" as including one or more, the limitation could be reasonably be interpreted as a sample coming from a single individual, rendering the claim indefinite.

13. In claims 4 and 20, applicant recites the limitation where the detectable label is selected from the group consisting of radioactive labels, non-radioactive labels and combinations thereof. It is unclear how a label can be both radioactive and non-

radioactive. Although applicant has defined the term "the" as including one or more, the limitation could be reasonably be interpreted as a single label or each label being a combination of radioactive and non-radioactive, rendering the claim indefinite.

14. In claim 5, applicant recites the limitation where the antibody is a monoclonal antibody, a polyclonal antibody, or combinations thereof. It is unclear how an antibody can be both a monoclonal antibody and a polyclonal antibody. Although applicant has defined the term "the" as including one or more, the limitation could be reasonably be interpreted as each antibody being a combination of monoclonal and polyclonal, rendering the claim indefinite.

15. The remainder of the claims are deemed indefinite due to their dependence on an indefinite claim.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claim 1 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian

FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In the application, the usherin protein of claim 1 is defined as having a polynucleotide complement capable of hybridizing to the polynucleotide represented by SEQ ID NO: 3, applicant has only specifically disclosed the polypeptides represented by SEQ ID NO: 1, 2, and 4. However, different polynucleotide sequences can encode the amino acid sequence encoded by polynucleotide sequence of SEQ ID NO: 3. Furthermore, frame shifts or polynucleotide complements that hybridize to different regions of SEQ ID NO: 3 would result in entirely different "usherin proteins", which are not disclosed by applicant. Applicant has not disclosed just any polynucleotide with a polynucleotide complement that hybridizes to SEQ ID NO: 3 that encodes a polypeptide, having the identical function of SEQ ID NO: X (i.e., the usherin protein). The instant disclosure of a single species of nucleic acid (SEQ ID NO: 3) does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides with complements that hybridize to SEQ ID NO: 3. There is no description of the conserved regions, which are critical to the structure and

function of the genus claimed. The specification proposes to discover other members of the genus by using hybridization to SEQ ID NO: 3. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure.

Polynucleotides that hybridize to SEQ ID NO: 3 and are not 100% identical can be interpreted as allelic variants of SEQ ID NO: 3. The general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of unknown variants. Reiger et al. (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO: 3, a skilled artisan cannot envision the detailed structure of the encompassed structurally and functionally disparate polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Thus, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed. Therefore, only polynucleotide complements of polynucleotides that encode the polypeptide sequences set forth in SEQ ID NOs: 1, 2, 4, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

18. Claim 1 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody immunoreactive with SEQ ID NO: 1, 2 and 4, does not reasonably provide enablement for an antibody immunoreactive with polypeptides that are less than 100% identical with SEQ ID Nos 1, 2 and 4 and polynucleotides encoding such.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In particular, while a person of ordinary skill in the art would know to use antibodies immunoreactive with the polypeptides of SEQ ID NO: 1, 2, and 4, there are other polypeptide sequences that have not been disclosed which a person of ordinary skill in the art would not know what antibodies to use.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a method comprising the step of incubating a biological sample with at least one antibody immunoreactive with a polypeptide, where the complement of the polynucleotide encoding the polypeptide is capable of hybridizing to the polynucleotide represented by SEQ ID NO: 3. The specification, however, only discloses the polypeptides of Seq ID NOs 1, 2, and 4.

As currently only SEQ ID NOs 1, 2, and 4 have been disclosed, only antibodies immunoreactive for those polypeptides have been provided. However, polynucleotides with complements that hybridize to SEQ ID NO: 3 encompass polypeptides that are less than 100% identical and antibodies that react with SEQ ID NOs 1, 2 and 4, would not necessarily react with polypeptides that are less than 100% identical to SEQ ID Nos. 1, 2 and 4. Colman [Colman, Effects of amino acid sequence changes on antibody-antigen interactions, 1994, Res Imm, 145, 33-36] and Lederman et al [Lederman et al, A single amino acid substitution in a common African allele of the CD4 molecule ablates binding of the monoclonal antibody, OKT4] teach amino acid substitutions may abolish or significantly reduce antibody binding. As can be seen, even a difference of a single amino acid could potentially necessitate the use of different, undisclosed antibodies.

The specification does not teach a method of determining whether an individual has or is at risk for developing Usher syndrome type IIa using antibodies that bind SEQ ID Nos. 1, 2 and 4 to bind polypeptides encoded by polynucleotides that hybridize to SEQ ID No:3 that are less than 100% identical to SEQ ID Nos. 1, 2 and 4. Insufficient direction or guidance and no working examples are provided to assist one skilled in the art to make and use the claimed antibodies that bind polypeptides that are less than 100% identical to SEQ ID Nos. 1, 2 and 4 that are encoded by polynucleotides that hybridize to SEQ ID NO:3 in a method of modulating the expression of Fos in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

In view of the lack of predictability of the art to which the invention pertains as evidenced by Coleman and Lederman et al and lack of guidance in the specification related to providing antibodies that specifically react with polypeptides encoded by polynucleotides with complements that hybridize to SEQ ID NO: 3, thereby forming an immunoconjugate which could be correlated with the presence or absence of Usher syndrome type IIa, undue experimentation would be required to practice the claimed method with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention and absent working examples providing evidence which is reasonably predictive that the claimed method is effective for polypeptides encoded by polynucleotides with complements capable of hybridizing to the polynucleotide sequence of SEQ ID NO: 3.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1-7, 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hursting et al [US 5,830,681] in view of Eudy et al [Eudy et al, Mutation of a gene encoding a protiein with extracellular matrix motifs in usher syndrome type IIa, 1998, Science, 280, 1753-1757].

21. With respect to claims 1 and 15, Hursting et al teach a method comprising obtaining a biological sample, incubating the biological sample with a first and second antibody immunoreactive with at least a portion of a protein under conditions effective to produce an immunoconjugate if the protein is present (column 7, lines 1-15), evaluating for the presence or absence of the immunoconjugate, and correlating the presence or absence of the immunoconjugate with a disease (column 7, lines 40-56). Hursting et al do not specifically teach the evaluation of an antibody that is immunoreactive with a protein, wherein a complement of a polynucleotide encoding the protein is capable of hybridizing to the polynucleotide represented by SEQ ID NO: 3, nor do Hursting et al teach the correlation of the presence of the immunoconjugate with Usher syndrome type IIa. Eudy et al, however, teach a gene encoding for SEQ ID: 3, with 99.6% homology (USH2A gene) is associated with Usher syndrome type IIa (p.1756, lines 15-21 and 50-55), and identification of the USH2A gene would lead to the development of a differential diagnostic tool for patients with Usher syndrome (p.1756, lines 50-55). Therefore, it would have been obvious to use an antibody immunoreactive with at least a portion of usherin, as taught by Eudy et al, and correlate the presence or absence of the resulting immunoconjugate with Usher syndrome type IIa in the method of Hellstrom et al, in order to develop a differential diagnostic tool for patients with Usher syndrome.

22. With respect to claim 2, Eudy et al teach the existence of studies involving determining the presence and distribution of USH2A protein in biological samples (the cochlea and retina) (p.1756, lines 56-65).

23. With respect to claims 3 and 17, Hursting et al teach that at least one antibody with an attached detectable label (column 7, lines 1-7).

24. With respect to claims 4 and 18, Hursting et al teach a radioactive detectable label (radioisotope) (column 7, lines 40-56).

25. With respect to claim 5, Hursting et al teach a monoclonal antibody attached to a solid surface (column 7, lines 9-10), and a polyclonal antibody with an attached detectable label (column 7, lines 5-8, 13).

26. With respect to claims 6 and 22, Hursting et al teach the use of an antibody immunoreactive with a polypeptide, as discussed above in paragraphs 20-21. Although Hursting et al do not specifically teach an antibody immunoreactive with a polypeptide selected from the group consisting of SEQ ID NOs: 1, 2, and 4, Eudy et al, however, do teach a polypeptide selected from the group consisting of SEQ ID NO: 1, 2, and 4 (p.1755, fig.4). Eudy et al, further teach that identification of the USH2A gene would lead to the development of a differential diagnostic tool for patients with Usher syndrome (p.1756, lines 50-55). Therefore it would have been obvious for a person of ordinary skill in the art to use an antibody immunoreactive with a polypeptide selected from the group consisting of SEQ ID NOs: 1, 2, and 4, as disclosed by Eudy et al, in order to develop a differential diagnostic tool for patients with Usher syndrome.

27. With respect to claims 7 and 23, Eudy et al teach a polynucleotide with 99.6% homology to the polynucleotide encoding the usherin protein represented by SEQ ID NO: 3. Although not identical, a person of ordinary skill in the art could reasonably assume that the polynucleotide sequences are not substantially different, particularly since the resulting polypeptide taught by Eudy et al has 100% homology with the polypeptide selected from the group consisting of SEQ ID NOs: 1, 2, and 4.

28. With respect to claim 16, a sandwich comprising the first antibody, the second antibody, and a protein is taught by Hursting et al (column 7, lines 40-56). Therefore, it would have been obvious, as discussed above in paragraph 21, for a person of ordinary skill in the art to specifically form a sandwich comprising the first antibody, the second antibody, and the usherin protein taught by Eudy et al.

29. With respect to claim 19, Hursting et al teach a monoclonal antibody (column 7, lines 5-15).

30. With respect to claim 20, Hursting et al teach a monoclonal antibody attached to a solid surface (column 7, lines 9-10), and a polyclonal antibody with an attached detectable label (column 7, lines 5-8, 13).

31. With respect to claim 21, Hursting et al teach a radioactive detectable label (radioisotope) (column 7, lines 40-56).

Conclusion

32. No claims are allowed.

33. The following references are also cited as art of interest: Eudy et al [Eudy et al, Molecular genetics of Usher syndrome, 1999, Cell Mol Life Sci, 56, 257-267], Sakashita et al [US 5,439,830], Skibbens et al [US 5,980,892], Brenner et al [US 5,747,036], Sakashita et al [US 5,439,830], Hellstrom et al [US 5,171,665], Hellstrom et al [US 5,134,075].

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

35. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

36. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Nelson Yang

Patent Examiner
Art Unit 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
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01/01/04